A Rare Case of *Brucella canis* in an HIV-Infected Patient

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Presentation: A 46-year-old HIV-infected woman was admitted with a three-day history of high fever, diffuse arthralgias, malaise, and loose stools.

History: The patient had been diagnosed with HIV infection for 16 years with no previous AIDS-defining diagnoses or other complications. A self-imposed, four-year treatment interruption and multiple failures of contemporary HIV treatment regimens, due to medication intolerance, led to restarting a previous effective regimen of didanosine, lamivudine, and boosted indinavir six months prior to admission. Her viral load one month prior to admission was non-detectable (<50 copies/mL) and CD4 count was 381. For 5 months prior to admission, she had intermittently complained of low-grade fevers, low back pain along with other arthralgias and myalgias, night sweats, fatigue, and hair loss. Evaluation during this time, including comprehensive metabolic panel, CBC, TSH, serology for coccidioidomycosis, RPR, pregnancy test, and CXR, were unremarkable. Three days prior to admission she was noted to have an elevated erythrocyte sedimentation rate of 69 mm/hr (normal range, 0-20 mm/hr) and C-reactive protein of 4.93 mg/dL (normal, 0-0.5 mg/dL) with a negative rheumatoid factor and ANA. Serum bicarbonate level was 21 mmol/L (normal, 22-29 mmol/L) and lactic acid level was 2.2 mmol/L (normal, 0.5-2.2 mmol/L)

Her past medical history was significant for childhood repair of a patent ductus arteriosis and depression. She worked as a warehouse clerk, denied tobacco or alcohol use, and always used condoms during intercourse. She lived in Arizona for 20 years and resided with her HIV-infected fiancé, daughter, and granddaughter. She was involved with animal husbandry and lived in the suburbs with five dogs and six horses.

Physical Exam: On admission she appeared well. The weight was 46.3 kg, the height 142 cm, the blood pressure 165/60, the pulse 103, and the temperature 39.4° C. Her physical examination revealed no abnormalities.

Initial test results: Comprehensive metabolic panel (other than a serum bicarbonate level of 21), CBC, routine blood cultures, serology for Epstein-Barr virus, and stool studies, were unrevealing.

Differential Diagnosis:

- Drug reaction: Multiple non-specific constitutional symptoms have been reported with most antiretrovirals. Nucleoside analogs have been associated with lactic acidosis and steatohepatosis. While she did not have elevated transaminases, the borderline lactic acidosis was of concern.
- Fungal infection: Coccidioidomysosis (cocci) is frequently in the differential diagnosis of febrile illnesses in central and southern Arizona. Seen mostly in recent arrivals to the area, it presents mostly with pulmonary and non-specific viral-like symptoms. Disseminated cocci is always a concern in HIV-infected individuals in the area, but was felt unlikely given her CD4 count and negative serology. *Cryptococcus neoformans* can present with only unexplained fevers and malaise. There was no history of travel to areas

endemic for histoplasmosis. Standard serologic testing was done to rule out fungal infection, despite a low index of suspicion.

- Bacterial: Disseminated *Mycobacterium tuberculosis* and *Mycobacterium avium* seemed unlikely given her CD4 count and normal CXR. *Salmonella* infections in HIV-infected patients may present more frequently with bacteremia and may have a paucity of gastrointestinal manifestations.(1)
- Viral: Systemic viral infections such as Epstein-Barr virus and parvovirus B19 were considered less likely given the duration of her symptoms.
- Zoonotic diseases: *Brucella melitensis* presents with a clinical picture consistent with that of our patient, however there was no exposure to goats, livestock, or unpasteurized milk. Ehrlichiosis, Campylobacter, Giardia, Listeriosis, Q fever, *Rhodococcus equi* all could be carried by a dog or horse but seemed unlikely based on the social history, disease transmission, and disease state of the patient and her animals.
- Endocarditis: Bacterial endocarditis was considered due to the elevated inflammatory markers and fever. However, no murmur or other physical manifestations were noted. Blood cultures and echocardiogram were ordered.
- Malignancy: Non-Hodgkin's lymphoma may present with any level of immunodeficiency and may present with fever and nightsweats. Computerized tomography (CT) of the thorax, abdomen, and pelvis were ordered.

Hospital Course: Antiretrovirals were discontinued. Acetaminophen was administered for the arthralgias and fever. The patient continued to have low-grade fevers and loose stools but overall felt better. The CT revealed borderline hepatomegaly with diffuse fatty infiltration and splenomegaly with a low-density lesion presumably representing a splenic infarct. The echocardiogram was normal. A rheumatology consultant did not feel a collagen vascular or other rheumatologic process was likely. The patient was discharged on the fourth hospital day with a diagnosis of possible drug reaction.

Conclusive test: The day following discharge of the patient, the hospital lab reported a slow growing gram-negative rod in one bacterial blood culture, eventually reported as a *Brucella* species. The isolate was transferred to the Arizona State Health Laboratory (ASHL) for speciation. Biochemical and molecular testing at the ASHL initially identified *Brucella melitensis*. Epidemiology staff from the Maricopa County Department of Public Health and the State Public Health Veterinarian interviewed the patient. The patient denied history of consumption of unpasteurized dairy products, contact with livestock or exposure to attenuated brucellosis vaccine. The patient did own seven dogs, one of which a veterinarian had screened for brucellosis due to infertility. A serologic test at a commercial veterinary diagnostic laboratory was positive, but was reported as negative on subsequent serology at Cornell University College of Veterinary Medicine's Animal Health Diagnostic Center.

Due to the history, additional testing of the patient's isolate was conducted at the ASHL and gel formation tests were positive for *Brucella canis*. Blood cultures were collected from all seven dogs and one of the other dogs was positive for *Brucella canis*. Both isolates were shipped to the Special Pathogens Branch of the Centers for Disease Control and Prevention, where the presence of *B canis* was confirmed. The isolates were also shipped to the National Animal Disease Center in Ames, Iowa, where the isolates were compared by strain typing via multi-locus analysis of variable number tandem repeats.(2) The DNA fingerprints were not identical, but the strains of *B canis* were felt related. The differences in the strain type may have been due to progressive microevolution, as the patient was infected up to 8 months prior to the collection of blood from the dog.

Diagnosis: Brucellosis due to *Brucella canis.*

Treatment: Since this patient's HIV medications were discontinued prior to hospital discharge, serious drug-drug interactions with rifampin were avoided and the infection was treated with a six-week course of doxycycline 200 mg/day plus rifampin 600 mg/day. An alternate regimen of doxycycline plus streptomycin was considered, however, medication compliance concerns with a daily injection made this option less feasible.

Clinical course: The patient was fully compliant with her treatment, and experienced complete resolution of her symptoms. Subsequently, she was placed on tenofovir, emtricitabine, and fosamprenavir and has responded to and tolerated this regimen without difficulty.

Discussion: In the last ten years, 50 cases of brucellosis, mostly *B melitensis* have been reported in humans in Arizona, this being the first reported human case of *B canis*.(3) Approximately 100 cases of brucellosis are reported to the CDC per year.(4) Approximately 1% of those are estimated to be caused by *B canis*. To our knowledge, this is the first case reported in an HIV-infected individual.

Brucellosis is a rare, but important zoonotic infection that may present with non-specific, constitutional symptoms and may be mistaken for adverse drug reactions. It is transmitted to humans by ingestion of raw dairy products, direct contact with an infected animal or inhalation of aerosols. Because the National Brucellosis Eradication Program has nearly eliminated *Brucella* infection from U.S. cattle herds, the majority of U.S. cases of brucellosis occur among returned travelers or recent immigrants from areas in which *Brucella* species are endemic.(4) Veneral transmission has been reported between a laboratory worker and his spouse.(5) Incubation typically takes 1-8 weeks after exposure and the history of possible exposures over the preceding few months is important. Our case emphasizes the importance of taking a detailed social and occupational history and maintaining domestic zoonoses in the differential diagnosis. As HIV is typically considered an "urban disease" and brucellosis is considered a "rural disease," it may be readily overlooked as the etiology of a febrile illness.(6)

References:

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